Remarks

No claims have been amended. New claim 54, which finds representative support in original claim 15 and paragraph [0019] of the published application, has been added. Applicants submit that no prohibited new matter has been introduced by the new claim.

1. Rejection under 35 U.S.C. 101

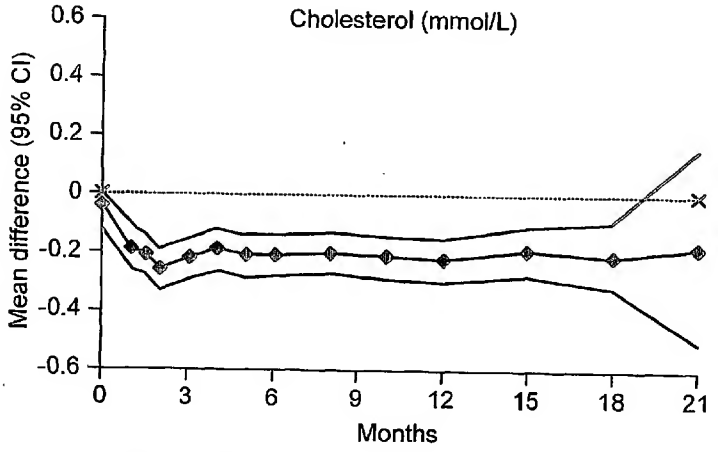
Claims 14, 16 and 18-21 are rejected for allegedly lacking patentable utility for the reasons asserted on pages 2-7 of the Office Action. The Examiner's basic argument against utility appears to be that the test data described in Applicant's specification was based on comparison to a "non-control" – *i.e.*, a compound (warfarin) not known to be a cholesterol-lowering agent – and as such, the test data does not meet the three-prong requirement of utility that it be specific, substantial and credible.

Applicants respectfully submit that the Examiner has both misinterpreted the experimental data presented in the subject application and elevated the level of proof required to establish utility under U.S. patent law above that set forth in the MPEP and established by U.S. courts.

Regarding the presented experimental data, the Examiner asserts that there is no evidence of lipid lowering until month 18 of treatment with ximelagatran. In rebuttal to this assertion, Applicant points to the passage at page 20, line 26 to page 21, line 5 of the application as filed, which describes the results of the clinical trial in relation to lipid / cholesterol lowering. The most important sentence from this passage states the following:

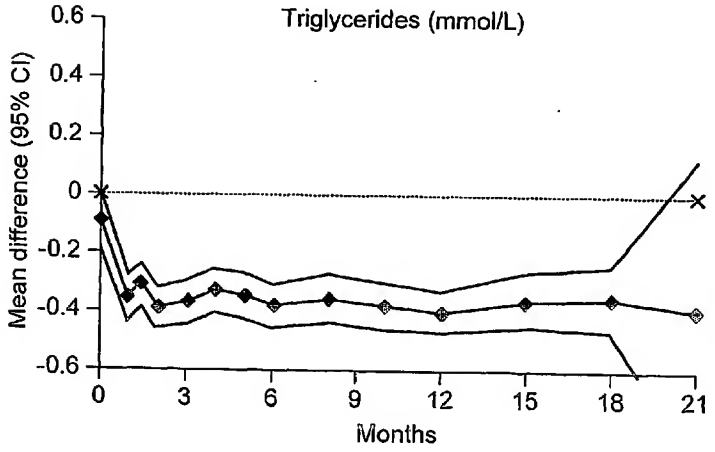
> As of the second month of treatment, marked mean differences were observed for cholesterol, triglycerides and LDL serum concentrations **(consistently significantly lower in the ximelagatran group over the entire 21 month period)** and for the HDL serum concentration **(consistently significantly higher in the ximelagatran group over the entire 21 month period)**, as illustrated in Figures 1 to 4, respectively (page 20, line 26 to page 21, line 5, emphasis added)

Applicant submits that the above passage unambiguously shows that the therapeutic effects observed with ximelagatran occurred over the entire 21 month dosing period. The Examiner's attention is directed to the data points in Figures 1 to 4.



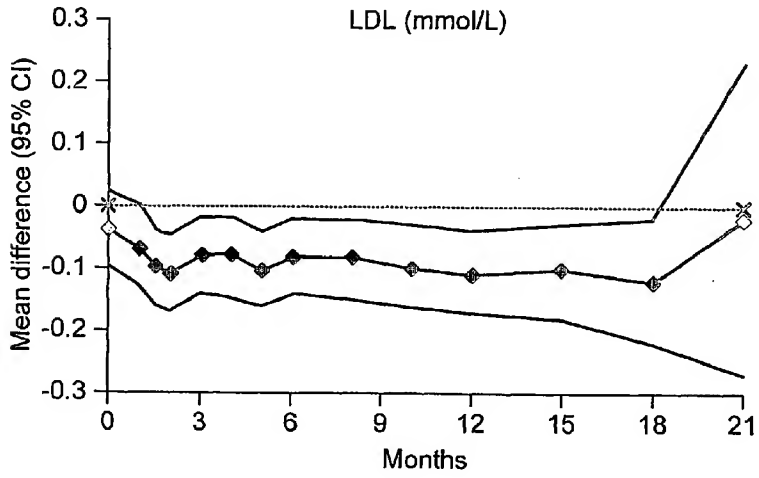
Mean at baseline: ximelagatran 5.27, warfarin 5.32

FIG. 1



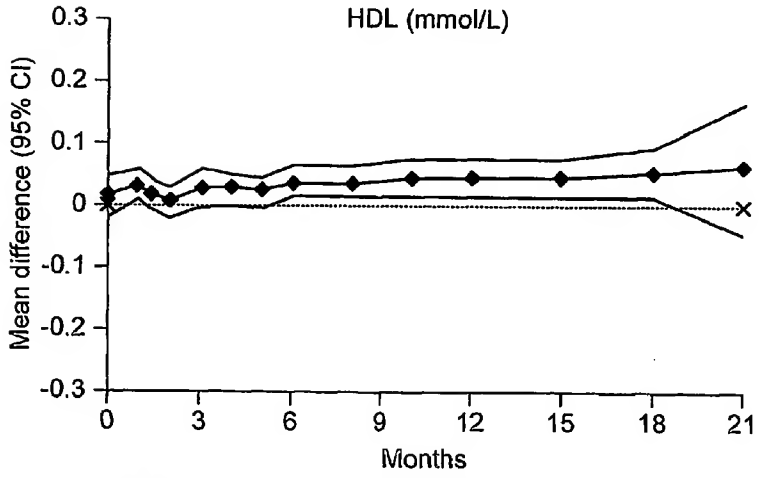
Mean at baseline: ximelagatran 1.86, warfarin 1.95

FIG. 2



Mean at baseline: ximelagatran 3.14, warfarin 3.18

FIG. 3



Mean at baseline: ximelagatran 1.31, warfarin 1.28

FIG. 4

These data points (depicted as black diamonds) provide the mean results of the 1,704 patients in the ximelagatran arm of the trial. Those results are represented as the differences (at 95% confidence intervals) in lipid levels in comparison to the mean results for the 1,703 patients in the warfarin arm of the trial. Figures 1 to 4 clearly demonstrate that

(i) mean cholesterol, triglyceride and LDL-cholesterol levels are consistently lower for the patients in the ximelagatran arm over the entire course of the trial (as evidenced by the black diamonds in Figures 1-3); and

(ii) mean HDL-cholesterol levels are consistently higher for the patients in the ximelagatran arm over the entire course of the trial (as evidenced by the black diamonds in Figure 4).

The Examiner has questioned the credibility of the results of the clinical trial, apparently upon the basis that the patients in the control arm were administered a drug (warfarin) that is not known to have any effect upon cholesterol levels. Applicants respectfully disagree for at least the following reasons.

First, and as indicated at the beginning of Example 1, the clinical trial in question was initially conducted to demonstrate the efficacy of ximelagatran as an anticoagulant (in this particular case, as an agent for the prevention of strokes in patients having non-valvular atrial fibrillation (NVAF). At the time the trial was designed, it was known that warfarin (another anticoagulant) was used to treat patients with NVAF. It is for that reason that warfarin was administered to patients in the "control" arm of the trial (with a view to obtaining data showing that ximelagatran was non-inferior to warfarin in the treatment of NVAF).

However, once the data from the trial was analyzed (including data from blood samples taken from patients at regular intervals during the trial), it was unexpectedly discovered that ximelagatran not only acted as an anticoagulant but also produced sustained and significant changes in lipid levels (in comparison to patients receiving warfarin). Although the clinical trial was not designed with the aim of proving the effect of ximelagatran on lipid levels, the data obtained from the trials are nevertheless sufficient to establish that ximelagatran does indeed produce beneficial changes in lipid levels (and is therefore useful as a cholesterol-lowering agent).

With regard to the choice of the drug to administer to patients in the control arm of the trial, Applicants point out that it is **irrelevant** whether or not warfarin is known to act as a cholesterol-lowering agent. What is relevant, however, is that ximelagatran has been demonstrated to provide beneficial changes in lipid levels in patients, in comparison to a "no effect" agent (*i.e.*, an agent such as warfarin that does not produce any effect on lipid levels in patients). Applicants again respectfully remind the Examiner that demonstrating a beneficial effect in comparison to a "no effect" agent (*e.g.*, a placebo) has long been an accepted way of demonstrating the clinical efficacy of a medicament.

Regarding the requirements for utility, Applicants submit that 35 U.S.C. 101 simply requires that an invention be useful, with no additional qualifications as to how useful it must be. Applicants reproduce below the actual wording of 35 U.S.C. 101:

> 35 U.S.C. 101 *Inventions patentable.*
> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

MPEP 2107.02 states that "[i]n most cases, an applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. 101. See, *e.g.*, *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (CCPA 1965); *In re Langer*, 503 F.2d 1380, 183 USPQ 288 (CCPA 1974); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977)." Further, MPEP 2164.07 states that "the applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." *In re Irons,* 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965). Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true."

In view of the above-discussed compelling and robust evidence provided in the subject application regarding the efficacy of ximelagatran as a cholesterol-lowering agent, Applicants

submit that the utility requirement has been satisfied and therefore respectfully request that this rejection be withdrawn.

2. Rejection under 35 U.S.C. 102(b)

Claims 14, 16 and 19-21 are rejected as anticipated by WO 02/036157 to Gustafsson ("Gustafsson") as evidenced by the Drug Reference and Kralova publications as asserted on pages 7-8 of the Office Action. In particular, the Examiner points to page 6, lines 1-10 of Gustafsson as explicitly teaching that thrombin inhibitors are acceptable for use in cholesterol-lowering therapy.

Applicants respectfully submit that the passage of Gustafsson cited by the Examiner as support for his assertion of a teaching of cholesterol-lowering therapy does not contain any reference to cholesterol-lowering therapy. As shown by the copy of page 6 of Gustafsson, submitted herewith for the Examiner's consideration, neither does any other section of page 6. "[A]nticipation under § 102 can be found only when the reference discloses exactly what is claimed…." (*Titanium Metals Corp. v Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985)). Because Gustafsson does not meet this requirement, Gustafsson cannot be held out as anticipating Applicants' claims.

The Examiner states on page 8 of the Office Action that "[f]urther evidence that the instantly claimed method of cholesterol-lowering therapy is not unobviously distinct from the method described in Gustafsson is…." Such a statement relates to the obviousness of Applicants' claimed invention and not to its novelty – therefore, this is an improper rejection under 35 U.S.C. 102(b) and should be withdrawn.

The Examiner also appears to focus on the similarities between the clinical trial described in the subject application and the clinical trial described in Gustafsson in rejecting Applicants' claims as lacking novelty. Applicants submit that the trial described in the subject application was *originally intended* to investigate the treatment of NVAF described in Gustafsson. However, it was unexpectedly discovered from analyzing blood samples taken from patients enrolled in the trial that, in addition to providing an anticoagulant effect, ximelagatran surprisingly produced sustained, significant and beneficial changes in lipid levels.

The subject application therefore describes (and claims) a completely new medical treatment that represents the practical application of an unexpected discovery arising from the clinical trial. However, it appears that the Examiner is relying on hindsight in comparing the disclosure of Gustafsson to the disclosure of the subject application, which is directed to a completely different invention.

3. Conclusion

The foregoing amendments and remarks are made to place the application in a condition for allowance. Applicants respectfully request reconsideration and the timely allowance of the pending claims. The Examiner is invited to telephone the undersigned to advance prosecution of the application.

Except for issue fees payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. 1.16 and 1.17 which may be required, including any required extension of time fees, or to credit any overpayment to Deposit Account No. 50-0310.

Respectfully submitted,
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patients with, or at risk of, NVAF. The skilled person will appreciate that patients with NVAF who are at risk of stroke include elderly patients generally (e.g. those with an age of greater than 75 years); patients with complicating health factors, such as hypertension, left ventricular dysfunction (e.g. left ventricular ejection fraction (LVEF) of less than 40%), symptomatic congestive heart failure, diabetes mellitus (especially in those patients of 65 years of age or greater) and/or coronary heart or artery disease (especially in those patients of 65 years of age or greater); and/or patients with a history of stroke, TIA and/or systemic embolism, all of which factors may predispose such patients to stroke and/or thromboembolic events.

Melagatran, and derivatives thereof, may be administered for systemic delivery using appropriate means of administration that are known to the skilled person.

Thus, in accordance with the invention, melagatran, and derivatives thereof, may be administered orally, intravenously, subcutaneously, buccally, rectally, dermally, nasally, tracheally, bronchially, topically, by any other parenteral route, or *via* inhalation, in the form of a pharmaceutical preparation comprising the active ingredient in a pharmaceutically-acceptable dosage form. Depending on the disorder, and the patient, to be treated, as well as the route of administration, the compositions may be administered at varying doses.

Preferred modes of delivery are systemic. For melagatran, preferred modes of administration are parenteral, more preferably intravenous, and especially subcutaneous. For prodrugs of melagatran, preferred modes of administration are oral.